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(54) Amide compounds, process for preparing the same, and composition for activating gastric motor function containing the same.

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(73) Proprietor : Hokuriku Pharmaceutical Co.,Ltd
1-Chome, 3-14 Tatekawacho Katsuyamashi
Fukui (JP)

(72) Inventor : Itoh, Yasuo
3-11-14 Motomachi Katsuyamashi
Fukui (JP)
Inventor : Kato, Hideo
3-5-8 Kentoku Fukushi
Fukui (JP)
Inventor : Koshinaka, Eiichi
2-6-3 Asahicho Katsuyamashi
Fukui (JP)
Inventor : Ogawa, Nobuo
2-6-5 Ashicho Katsuyamashi
Fukui (JP)
Inventor : Nishino, Hiroyuki
23-14 Matta Aradocho Katsuyamashi
Fukui (JP)
Inventor : Sakaguchi, Jun
3-5-10 Asahicho Katsuyamashi
Fukui (JP)

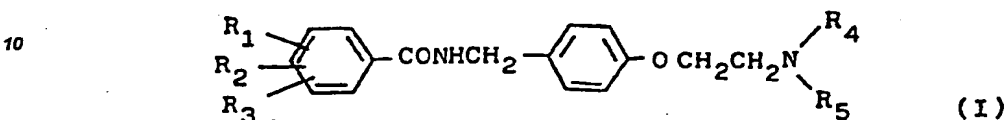
(74) Representative : Werner, Hans-Karsten, Dr. et
al
Deichmannhaus am Hauptbahnhof
W-5000 Köln 1 (DE)

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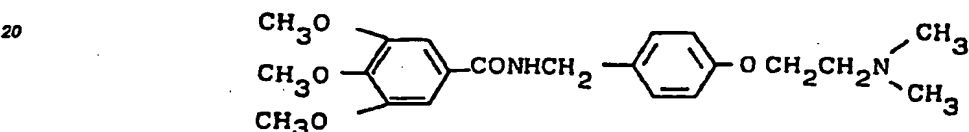
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Description**1. Field of the Invention**

5 The present invention relates to novel amide compounds represented by the following general formula (I) as well as acid addition salts thereof, process for preparing the same, and a composition for activating gastric motor function containing the same as active ingredient which can be used in the treatment of related ailments.

**2. Description of the Prior Art**

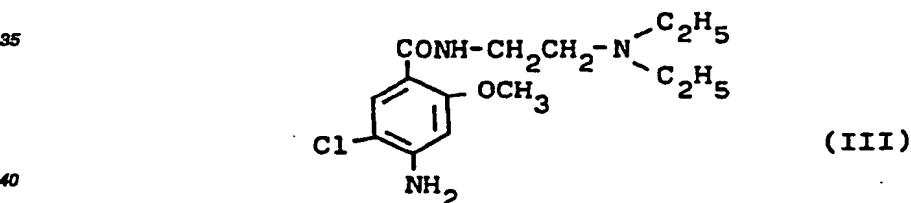
15 It is already known that N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide [general name, TRIMETHOBENZAMIDE, The United States Pharmacopeia XXI, 1094 (1985)] represented by formula (II),



25 can be used only as an antiemetic drugs and is not used for activating gastric motor function.

Non-ulcer dyspepsia such as gastric discomfort and abdominal distension results in part from a decrease of gastric motor function. Therefore, it is necessary to administer a drug which has the action on activating gastric motor function, so that such symptoms can also be alleviated.

30 So far, as a medicament which has the action on activating gastric motor function, 4-Amino-5-chloro-N-[(2-diethylamino)ethyl]-2-methoxybenzamide (general name, Metoclopramide, The Merck Index 10th Edition, 6019) represented by formula (III) is known.

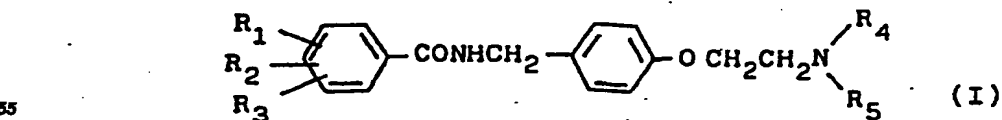


But this medicament has also the antiemetic effect. Medicaments such as this one are not satisfactory for practical use because of insufficient efficacy and having the serious side effects.

45 Accordingly, there has been a need for a new and useful medicament for the activation of the gastric motor function.

3. Summary of the invention

50 It has been found surprisingly, that the amide compounds represented by the formula (I):



wherein R₁ represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted

by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R_2 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, wherein R_1 and R_2 can be combined to form methylenedioxy, R_3 means hydrogen, lower alkyl, halogen, or amino, R_4 and R_5 may be the same or different and each represents lower alkyl or wherein R_4 and R_5 may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, and pharmacologically-acceptable acid-addition salts thereof, exhibit excellent effects in the activation of gastric motor function.

Further, according to the present invention, there are provided also a process for preparation of the novel amide compounds represented by the general formula (I), pharmaceutical compositions useful to activate gastric motor function comprising one or more compounds as represented by the formula (I) in an amount effective for such purpose, as well as a method for the treatment of a subject suffering from an ailment associated with inadequate gastric motor function by administering such a compound to the said subject.

DETAILED DESCRIPTION OF THE INVENTION

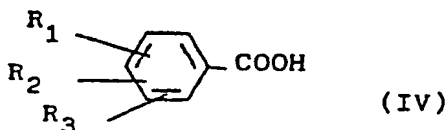
By the term "lower" in formula (I) is meant a straight or branched carbon chain having 1-4 carbon atoms, inductively. Therefore the lower alkyl moiety of the lower alkyl group encompassed by R_1 , R_2 , R_3 , R_4 and R_5 is representatively methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc. The lower alkoxy moiety of the lower alkoxy group is representatively methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, etc. As halogen represented by R_1 , R_2 and R_3 can be used: fluorine, chlorine and bromine, etc. Examples of amine, which may be substituted by lower alkyl are amino, methylamino, dimethylamino, and diethylamino, etc. and examples of sulfamoyl group, which may be substituted by lower alkyl are sulfamoyl, methylaminosulfonyl and dimethylaminosulfonyl, etc.

The compounds represented by the formula (I) can be converted to their pharmacologically-acceptable acid-addition salts in the usual manner and the free base can be liberated from the resulting salts if desired.

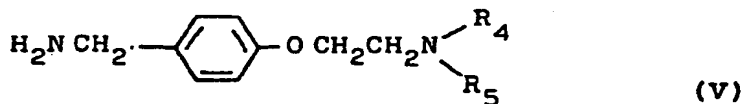
Pharmacologically-acceptable acid-addition salts of the amide compounds represented by the formula (I) include, for example, mineral salts such as hydrochloride, hydrobromide, nitrate, sulfate, phosphate, and the like, or organic acid salts such as acetate, maleate, fumarate, citrate, oxalate, lactate, malate, tartarate, and the like.

The novel amide-compounds represented by the general formula (I) can be prepared as follows:

A functional derivative such as the chloride or other halide, the anhydride or a mixed anhydride, of a carboxylic acid represented by the formula (IV)



wherein R_1 , R_2 and R_3 each has the same meaning as described above, is reacted with an amino-compound represented by the formula (V)



wherein R_4 and R_5 each has the same meaning as described above, in the presence or absence of a base and in the presence of an inert organic solvent.

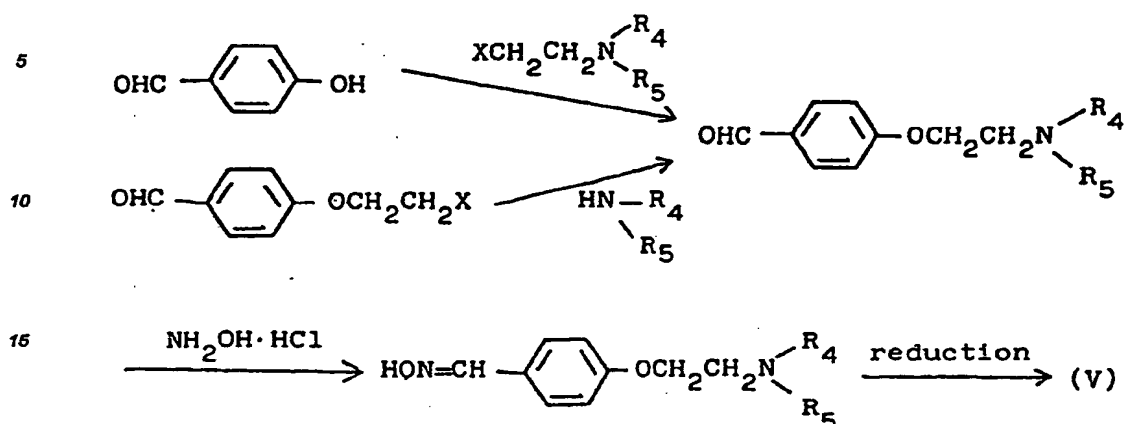
Bases which can be used in this method are, for example, pyridine, picoline, lutidine, collidine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, triethylamine, potassium carbonate, sodium carbonate, or the like.

The solvent used in this reaction can be any kind of solvent which does not inhibit the reaction. Examples of the inert organic solvent which may be used are ether, benzene, toluene, ethyl acetate, tetrahydrofuran, dioxane, chloroform, methylenechloride, dimethylsulfoxide, and N,N-dimethylformamide.

The reaction is generally carried out at a temperature within the range of 0°C to the reflux temperature of the reaction solvent employed.

The starting materials represented by the above formula (V), most of which are novel compounds, can be

prepared by a process shown in the following scheme :



wherein R_4 and R_5 each has the same meaning as described above and X represents a halogen.

The most important compounds of this invention are for example as follows :

N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide, N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride, 3,4-Methylenedioxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl] benzamide, 3,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide, N-[4-[2-(dimethylamino)ethoxy]benzyl]-4-ethoxy-3-methoxybenzamide, N-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamide, and 4-amino- 5-chloro-2-methoxy-N-[4-[2-(1-pyrrolidinyl) ethoxy]benzyl]benzamide.

A compound of the present invention represented by general formula (I) can be administered per os, e.g., in the form of pills or tablets, in which it may be present together with any of the usual pharmaceutical carriers, conventionally by compounding a compound of this invention together with a customary carrier or adjuvant, such as talc, magnesium stearate, starch, lactose, gelatin, any of numerous gums, or the like. Thus, in their most advantageous form, the compositions of this invention will contain a non-toxic pharmaceutical carrier in addition to the active ingredient of the present invention. Exemplary solid carriers are lactose, magnesium stearate, calcium stearate, starch, D-mannitol, crystalline cellulose, or the like. Representative liquid carriers are water, sesame oil, olive oil, propylene glycol, or the like. The active agents of this invention can be conveniently administered in such compositions containing active ingredient so as to be within the dosage range illustrated hereinafter. Thus, a wide variety of pharmaceutical forms suitable for many modes of administration and dosages may be employed. For oral administration, the active ingredient and pharmaceutical carrier may, for example, take the form of a powder, granule, pill, tablet, capsule, lozenge, elixir, syrup, or other liquid suspension or emulsion whereas, for parenteral administration, the composition may be in the form of a sterile solution. For intra-rectal administration, the composition may be in the form of a suppository.

The method of using the compounds of this invention comprises internally or externally administering a compound of this invention, preferably orally or parenterally and preferably admixed with the pharmaceutical carrier, for example, in the form of any of the above compositions, or filled into a capsule, to alleviate conditions to be treated and symptoms thereof in a living animal body. Illustratively, it may be used in an amount of about 1.0 to about 1000 mg per day for oral administration, and about 1.0 to about 500 mg per day for a parenteral administration. The unit dose is preferably given a suitable number of times daily, typically three times.

The unit dose may vary depending upon the number of times given in any time period. Naturally, a suitable clinical dose must be adjusted in accordance with the condition, age, and weight of the patient, and it goes without saying that the enhanced activities of the compounds of the invention, together with their reduced side effects, also make them suitable for wide variations, and this invention therefore should not be limited by the exact ranges stated. The exact dosage, both unit dosage and daily dosage, will of course have to be determined according to established medical principles.

The following experiments show with the excellent effect of the present compounds (Compound No. means Example Compound No.), while using metoclopramide hydrochloride (III HCl) and trimethobenzamide hydrochloride (II HCl) as reference compounds.

Experiment 1

Contractile effects of the test compounds in isolated guinea pig ileum

Male Hartley guinea-pigs weighing about 450 g were sacrificed and the ileum was excised. Then intact strips 1.5-2.0 cm long were prepared. These preparations were suspended vertically in an organ bath filled with Krebs-Henseleit's solution at 37°C which was gassed with 95% O₂ and 5% CO₂. Rhythmic contractions of the preparations were isotonically measured. Effects of the test compounds were assessed as the relative percentage of a test compound against 10⁻⁶M acetylcholine-induced contractions. Results were as follows (Table 1).

Table 1

Test compounds	ED ₅₀ (M) *
Compound 2	6.0 x 10 ⁻⁷
Compound 3	4.6 x 10 ⁻⁷
Compound 5	1.8 x 10 ⁻⁷
Compound 6	4.0 x 10 ⁻⁷
Compound 7	3.0 x 10 ⁻⁷
Compound 8	1.6 x 10 ⁻⁶
Compound 14	6.9 x 10 ⁻⁷
Compound 19	4.2 x 10 ⁻⁷
Compound 20	5.0 x 10 ⁻⁷
Compound 23	3.0 x 10 ⁻⁷
Compound 24	6.1 x 10 ⁻⁷
Compound 25	6.8 x 10 ⁻⁷
Compound 31	4.2 x 10 ⁻⁷
Compound 32	1.2 x 10 ⁻⁷
Compound 34	1.4 x 10 ⁻⁷
Compound 35	4.9 x 10 ⁻⁷
Compound 36	3.4 x 10 ⁻⁷
Compound 37	1.8 x 10 ⁻⁷
Compound 38	3.5 x 10 ⁻⁷
Compound 39	3.9 x 10 ⁻⁷
Compound 40	6.0 x 10 ⁻⁷
Compound 41	1.3 x 10 ⁻⁷
Compound 42	< 10 ⁻⁷
Compound 43	< 10 ⁻⁷
Compound 45	4.6 x 10 ⁻⁶
Compound 47	3.0 x 10 ⁻⁶
Compound 48	5.1 x 10 ⁻⁷
Compound 51	6.1 x 10 ⁻⁷
Compound 52	4.5 x 10 ⁻⁷
Compound 53	4.6 x 10 ⁻⁷
Compound 55	1.3 x 10 ⁻⁶
Compound 56	3.2 x 10 ⁻⁷
Compound 57	9.3 x 10 ⁻⁷
Compound 58	4.2 x 10 ⁻⁷
Compound 59	6.2 x 10 ⁻⁷
Compound 62	3.9 x 10 ⁻⁷
Compound 63	5.0 x 10 ⁻⁷
Metoclopramide HCl	6.3 x 10 ⁻⁶
Trimethobenzamide HCl	1.5 x 10 ⁻⁶

* The dose which evoked 50 % of the acetylcholine-induced contraction.

These results showed that compound 2 had about 10 times and about 2.5 times stronger contractile effect than metoclopramide · HCl and trimethobenzamide · HCl respectively.

Experiment 2

Improving effects of the test compound on dopamine-induced suppression of gastrointestinal transit in mice

Male mice of the ddY strain weighing about 22 g were fasted overnight and the test compounds (suspended in 0.5% carboxymethylcellulose) were administered orally. Thirty minutes later dopamine (2 mg/kg dissolved

in saline) or saline only was administered intraperitoneally followed immediately by the oral administration of charcoal meal (5% charcoal powder suspended in 10% gum arabic). Twenty minutes later the animals were sacrificed and the digestive tracts were isolated from the stomach to the cecum. The gastrointestinal transit was determined by calculating the total intestinal length between the pylorus and the cecum and the length over which charcoal meal was carried from the pylorus. Statistical analysis was carried out by Student's t-test for unpaired observations. Results were as follows (Table 2).

Table 2

Experimental group	Dose (mg/kg, p.o.)	n	Gastrointestinal transit (% \pm S.E.)	Improvement %
Control	—	10	53.3 \pm 2.0**	
Dopamine alone	—	12	31.7 \pm 3.2	
Compound 2 + Dopamine	30	11	43.9 \pm 2.8**	56.5
Control	—	11	53.3 \pm 2.0**	
Dopamine alone	—	12	31.7 \pm 3.2	
Compound 3 + Dopamine	30	10	44.0 \pm 4.7*	56.9
Control	—	10	50.1 \pm 3.0**	
Dopamine alone	—	10	25.0 \pm 3.4	
Compound 18 + Dopamine	30	10	43.0 \pm 6.5*	71.7
Control	—	12	51.8 \pm 1.7**	
Dopamine alone	—	13	35.9 \pm 2.1	
Compound 31 + Dopamine	30	12	45.2 \pm 3.0*	58.5
Control	—	10	54.5 \pm 3.4**	
Dopamine alone	—	10	32.9 \pm 3.1	
Compound 34 + Dopamine	30	11	46.6 \pm 3.4*	63.4
Control	—	22	50.9 \pm 2.1**	
Dopamine alone	—	22	32.1 \pm 2.0	
Metoclopramide + HCl + Dopamine	30	9	37.2 \pm 3.2	27.1
Control	—	22	50.9 \pm 2.1**	
Dopamine alone	—	22	32.1 \pm 2.0	
Trimethobenzamide + HCl + Dopamine	30	13	38.2 \pm 3.8	32.4

* and ** : Significantly different from groups treated with dopamine at P < 0.05 and P < 0.01, respectively.

It is concluded that the compounds of this invention showed significant improvement of gastrointestinal transit which was inhibited by dopamine at a dose of 30 mg/kg, but that the antiemetic drugs both metoclopramide · HCl and trimethobenzamide · HCl did not so only to a much lesser extent.

Experiment 3

Suppressing effects of the test compounds on apomorphine-induced emesis in beagle dogs

Male beagle dogs weighing about 8 kg were fasted overnight. The test compounds (suspended or dissolved in 0.5% CMC) were administered orally and the dogs fed fortyfive minutes later. Then, fifteen minutes later 100 mg/kg apomorphine (dissolved in saline) was administered subcutaneously and emetic events were observed for sixty minutes.

As a consequence, and as expected the antiemetic drugs metoclopramide HCl and trimethobenzamide · HCl showed the significant antiemetic effect at doses of 1 mg/kg and 30 mg/kg, respectively. The compound 2 shows however slight antiemetic effect at a dose of 30 mg/kg.

Experiment 4**Acute toxicological study in mice**

5 Male ICR mice aged 5 weeks were used for each determination. The test compounds (2-4 different doses) were intravenously administered and LD₅₀ values were calculated using the up and down method. Results were as follows (Table 3).

10

Table 3

15

Test compounds	LD ₅₀ (mg/kg)
Compound 2	190.6
Compound 3	62.6
Compound 5	94.0
Compound 6	39.2
Compound 8	85.1
Compound 19	70.8
Compound 23	74.1
Compound 25	87.1
Compound 31	104.7
Compound 32	112.2
Compound 34	44.7
Compound 35	61.7
Compound 47	68.5
Compound 48	83.2
Compound 51	85.9
Compound 53	77.6

45

50

The following prescriptive examples and examples are given by way illustration only and are not to be construed as limitations of this invention, many variations of which are possible without departing from the scope and spirit thereof.

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Prescriptive Example 1: Capsule Formulation (hard capsule)

	Compound of Example 2	50mg
5	Lactose	a proper quantity
	Corn Starch	20mg
	Magnesium Stearate	1mg

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to 130mg

15

Prescriptive Example 2: Tablet Formulation

	Compound of Example 5	50mg
	Lactose	a proper quantity
20	Corn Starch	20mg
	Magnesium Stearate	2mg
25	Hydroxypropylmethyl cellulose	8mg
	Polyethyleneglycol	1mg
	Titanium Oxide	1mg

30

to 210mg

35

Prescriptive Example 3: Granule Formulation

	Compound of Example 2	100mg
40	Lactose	a proper quantity
	D-Mannitol	500mg
	Hydroxypropyl cellulose	20mg
45	Talc	2mg

50

to 1000mg

55

Prescriptive Example 4: Injection Formulation

5

Compound of Example 6 (hydrochloride)	50mg
Citric acid	0.5mg
Sodium Hydroxide	a proper quantity
Distilled Water for Injection	a proper quantity

15

to 1ml

Prescriptive Example 5: Suppository Formulation

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Compound of Example 48 (hydrochloride)	50mg
Hard Fat	1250mg

25

to 1300mg

Reference 1

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4-[2-(Dimethylamino)ethoxy] benzaldehyde

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To a solution of 61.1 g of p-hydroxybenzaldehyde in 240 ml of N,N-dimethylformamide was added 138 g of potassium carbonate, 80.7 g of 2-dimethylaminoethyl chloride and 30 ml of isopropyl ether. The mixture was stirred at 60°C for 1.5 hours. After cooling, the reaction mixture was poured into 720 ml of water, and the whole was extracted with chloroform. The chloroform layer was extracted with aqueous hydrochloric acid. The aqueous layer was made alkaline with aqueous sodium hydroxide solution and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was distilled to give 69.1 g of colorless oil, b.p. 142-144°C (4 mmHg).

40

NMR spectrum δ (CDCl₃) ppm : 2.34 (6H, s), 2.76 (2H, t, J = 6Hz), 4.15 (2H, t, J = 6 Hz), 7.02 (2H, d, J = 9Hz), 7.82 (2H, d, J = 9Hz), 9.87 (1H, s).

Reference 2

45

4-[2-(1-Pyrrolidinyl)ethoxy]benzaldehyde

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A mixture of 2.29 g of 4-(2-bromoethoxy)benzaldehyde, 1.42 g of pyrrolidine and 2.07 g of potassium carbonate in 8 ml of N,N-dimethylformamide was stirred at 60°C for 2 hours. After cooling, water was added and the whole was extracted with ethyl acetate. The ethyl acetate layer was extracted with aqueous hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was distilled to give 1.72 g of colorless oil, b.p. 170°C (5 mmHg).

NMR spectrum δ (CDCl₃) ppm : 1.60-2.27 (4H, m), 2.44-2.80 (4H, m), 2.93 (2H, t, J = 6Hz), 4.19 (2H, t, J = 6Hz), 7.01 (2H, d, J = 9Hz), 7.82 (2H, d, J = 9Hz), 9.87 (1H, s).

55

In the same manner as described in Reference 1 and 2, the compound in Reference 3 was prepared.

Reference 3

4-(2-Piperidinoethoxy)benzaldehyde

5 Colorless oil, b.p. 160-162°C (6 mmHg).

NMR spectrum δ (CDCl₃) ppm : 1.12-1.76 (6H, m), 2.27-2.61 (4H, m), 2.79 (2H, t, J = 6Hz), 4.18 (2H, t, J = 6Hz), 7.00 (2H, d, J = 9Hz), 7.82 (2H, d, J = 9Hz), 9.87 (1H, s).

Reference 4

10

4-[2-(Dimethylamino)ethoxy]benzaldehyde

A mixture of 154 g of 4-[2-(dimethylamino)ethoxy]benzaldehyde and 59.9 g of hydroxylamine hydrochloride in 600 ml of ethanol was boiled for 10 minutes. After cooling, the precipitate was filtered to give hydrochloride as pale yellow crystals, m.p. 174-175°C. These crystals were dissolved in 150 ml of water. The solution was made alkaline with potassium carbonate and extracted with chloroform. The extract was dried and evaporated. The residue was washed with isopropyl ether to give 157 g of colorless crystals, which were recrystallized from ethyl acetate as colorless flakes, m.p. 95-96°C.

Analysis for C₁₁H₁₆N₂O₂ :

20 Calculated % : C, 63.44 ; H, 7.74 ; N, 13.45.

Found % : C, 63.28 ; H, 7.71 ; N, 13.37.

In the same manner as described in Reference 4, the compounds in References 5 and 6 were prepared.

25 Reference 5

4-[2-(1-Pyrrolidinyl)ethoxy]benzaldehyde hydrochloride :

Colorless plates, m.p. 219-220.5°C (EtOH).

30 Analysis for C₁₃H₁₈N₂O₂ · HCl :

Calculated % : C, 57.67 ; H, 7.07 ; N, 10.35.

Found % : C, 57.57 ; H, 7.15 ; N, 10.25.

Reference 6

35

4-(2-Piperidinoethoxy)benzaldehyde hydrochloride

Colorless flakes, m.p. 224-225°C (EtOH).

Analysis for C₁₄H₂₀N₂O₂ · HCl :

40 Calculated % : C, 59.05 ; H, 7.43 ; N, 9.84.

Found % : C, 58.74 ; H, 7.28 ; N, 9.64.

Reference 7

45

4-(2-Piperidinoethoxy)benzylamine

A suspension of 32.3 g of 4-(2-piperidinoethoxy)benzaldehyde in 400 ml of 10% methanolic ammonia was hydrogenated over 3.6 g of Raney nickel catalyst at a pressure of 50 kg/cm² and at 30°C. The catalyst was filtered off and the filtrate was evaporated. The residue was distilled to give 27.7 g of colorless oil, b.p. 185-190°C (6 mmHg).

50

NMR spectrum δ (CDCl₃) ppm : 1.30-1.90 (8H, m), 2.40-2.60 (4H, m), 2.76 (2H, t, J = 6Hz), 3.79 (2H, s), 4.09 (2H, t, J = 6Hz), 6.86 (2H, d, J = 9Hz), 7.21 (2H, d, J = 9Hz).

In the same manner as described in Reference 7, the compounds in References 8 and 9 were prepared.

55

Reference 8

4-[2-(1-Pyrrolidinyl)ethoxy]benzylamine

5 Colorless oil, b.p. 163-165°C (3 mmHg).

NMR spectrum δ (CDCl₃) ppm : 1.53 (2H, br), 1.70-1.90 (4H, m), 2.50-2.75 (4H, m), 2.89 (2H, t, J = 6Hz), 3.79 (2H, s), 4.10 (2H, t, J = 6Hz), 6.88 (2H, d, J = 9Hz), 7.22 (2H, d, J = 9Hz).

Reference 9

10

4-[2-(Dimethylamino)ethoxy]benzylamine

Colorless oil, b.p. 142-144°C (6 mmHg).

15 NMR spectrum δ (CDCl₃) ppm : 1.45 (2H, s), 2.32 (6H, s), 2.71 (2H, t, J = 6Hz), 3.79 (2H, s), 4.05 (2H, t, J = 6Hz), 6.88 (2H, d, J = 9Hz), 7.21 (2H, d, J = 9Hz).

Example 1

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide

20

To a cooled solution of 20.0 g of 4-[2-(dimethylamino)ethoxy]benzylamine in 60 ml of toluene was added a solution of 21.7 g of 3,4-dimethoxybenzoyl chloride (which was prepared with 19.7 g of 3,4-dimethoxybenzoic acid and 38.5 g of thionyl chloride in the usual manner) in 60 ml of toluene with stirring. The mixture was stirred at room temperature for 30 minutes. To the mixture was added 120 ml of water and 1 ml of concentrated hydrochloric acid.

25

The aqueous layer was separated, washed with 20 ml of toluene and made alkaline with 20% sodium hydroxide solution to give a precipitate, which was washed with isopropyl ether, of 37.0 g of pale brownish crystals. Recrystallization of the crystals from ethanol and isopropyl ether gave the title compound as colorless needles, m.p. 111-112°C.

30

Analysis for C₂₀H₂₆N₂O₄ :

Calculated % : C, 67.02 ; H, 7.31 ; N, 7.82.

Found % : C, 66.96 ; H, 7.28 ; N, 7.78.

Example 2

35

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride

A solution of 3.23 g of N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide in ethanol was acidified by the addition of ethanolic hydrogen chloride. The precipitate was filtered and washed with a mixture of ethanol and isopropyl ether to give 3.22 g of pale brownish crystals, which were recrystallized from ethanol as colorless prisms, m.p. 194-195°C.

40

Analysis for C₂₀H₂₆N₂O₄ · HCl :

Calculated % : C, 60.83 ; H, 6.89 ; N, 7.09.

Found % : C, 60.78 ; H, 6.99 ; N, 7.05.

45

Example 3

3,4-Methylenedioxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide :

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To a cooled solution of 20.0 g of 4-[2-(1-pyrrolidinyl)ethoxy]benzylamine in 30 ml of chloroform was added 17.7 g of 3,4-methylenedioxybenzoyl chloride (which was prepared with 15.9 g of piperonylic acid and 65.3 g of thionyl chloride in the usual manner). The mixture was stirred at room temperature for 20 minutes and the solvent was evaporated. 150 ml of water was added to the residue and the mixture was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was washed with isopropyl ether to give 30.0 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 93.5-94.5°C.

55

Analysis for C₂₁H₂₄N₂O₄ :

Calculated % : C, 68.46 ; H, 6.57 ; N, 7.60.
 Found % : C, 68.44 ; H, 6.65 ; N, 7.45.

Example 4

2,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide

To a cooled suspension of 1.82 g of 2,4-dimethoxybenzoic acid in 10 ml of tetrahydrofuran was added 1.09 g of ethyl chloroformate and 1.01 g of triethylamine. After stirring for 15 minutes, to the mixture was added a solution of 2.00 g of 4-[2-(1-pyrrolidinyl)-ethoxy]benzylamine in 5 ml of tetrahydrofuran. The mixture was stirred for 15 minutes and the solvent was evaporated. To the residue was added 10% hydrochloric acid, and the solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to give 3.31 g of the title compound as a colorless oil.

Mass spectrum m/z : 384 (M^+)

IR spectrum ν (liquid) cm^{-1} : 1648 (c = o)

NMR spectrum δ ($CDCl_3$) ppm ; 1.62-1.97 (4H, m),

2.44-2.76 (4H, m), 2.88 (2H, t, $J = 6$ Hz), 3.84 (3H, s), 3.86 (3H, s), 4.09 (2H, t, $J = 6$ Hz), 4.58 (2H, d, $J = 5.5$ Hz), 6.46 (1H, d, $J = 2$ Hz), 6.59 (1H, dd, $J = 9, 2$ Hz), 6.88 (2H, d, $J = 9$ Hz), 7.27 (2H, d, $J = 9$ Hz), 7.99 (1H, br), 8.21 (1H, d, $J = 9$ Hz).

Example 5

4-Amino-5-chloro-N-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxybenzamide

To a cooled suspension of 2.49 g of 4-amino-5-chloro-2-methoxy-benzoic acid in 15 ml of chloroform were successively added dropwise 1.26 g of triethylamine and 1.35 g of ethyl chloroformate with stirring. The mixture was stirred at the same temperature for 30 minutes. Next, to the mixture was added a solution of 2.00 g of 4-[2-(dimethylamino)ethoxy]benzylamine in 10 ml of chloroform with stirring. The mixture was stirred at room temperature for 14 hours and the solvent was evaporated. 10% Hydrochloric acid was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was washed with ether to give 3.87 g of slightly brownish crystals, which were recrystallized from ethanol to give colorless needles, m.p. 147-148°C.

Analysis for $C_{19}H_{24}ClN_3O_3$:

Calculated % : C, 60.39 ; H, 6.40 ; N, 11.12.

Found % : C, 60.28 ; H, 6.46 ; N, 11.12.

Further, the free base was converted into the hydrochloride in the usual way using ethanolic hydrogen chloride as in Example 2. Recrystallization of the hydrochloride from ethanol gave colorless needles, m.p. 206.5-208°C.

Analysis for $C_{19}H_{24}ClN_3O_3 \cdot HCl$:

Calculated % : C, 55.08 ; H, 6.08 ; N, 10.14.

Found % : C, 54.86 ; H, 6.21 ; N, 9.98.

Example 6

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamide

To a cooled suspension of 14.3 g of 2-methoxy-5-sulfamoylbenzoic acid in 60 ml of tetrahydrofuran were successively added dropwise 6.25 g of triethylamine and 7.45 g of pivaloyl chloride with stirring. The mixture was stirred at the same temperature for 1 hour and then a solution of 10.0 g of 4-[2-(dimethylamino)ethoxy]benzylamine in 40 ml of tetrahydrofuran was added dropwise with stirring. The mixture was stirred at room temperature for 14 hours and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate to give a precipitate, which was washed with water and ethyl acetate, of 16.6 g of colorless crystals. Recrystallization of the crystals from ethanol gave the title compound as colorless needles, m.p. 154-155°C.

Analysis for $C_{19}H_{25}N_3O_5S$:

Calculated % : C, 56.00 ; H, 6.18 ; N, 10.31.

Found % : C, 55.71 ; H, 6.21 ; N, 10.02.

5 Further, the free base was converted into the hydrochloride in the usual way. Recrystallization of the hydrochloride from methanol gave colorless needles, m.p. 122.5-123°C.

Analysis for $C_{19}H_{25}N_3O_5S \cdot HCl \cdot 2H_2O$:

Calculated % : C, 47.55 ; H, 6.30 ; N, 8.75.

Found % : C, 47.47 ; H, 5.90 ; N, 8.72.

10

Example 7

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-5-dimethylaminosulfonyl 2-methoxybenzamide

15 To a cooled suspension of 3.20 g of 5-dimethylaminosulfonyl-2-methoxybenzoic acid in 10 ml of tetrahydrofuran were successively added dropwise 1.25 g of triethylamine and 1.34 g of ethyl chloroformate with stirring. The mixture was stirred at the same temperature for 30 minutes and then a solution of 2.00 g of 4-[2-(dimethylamino)ethoxy]benzylamine in 10 ml of tetrahydrofuran was added dropwise with stirring. The mixture was stirred at room temperature for 2 hours and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was dried and evaporated. The residue was washed with isopropyl ether to give 4.10 g of colorless crystals, which were recrystallized from a mixture of ethyl acetate and ether to give colorless needles, m.p. 99.5-100.5°C.

25 Analysis for $C_{21}H_{29}N_3O_5S$:

Calculated % : C, 57.91 ; H, 6.71 ; N, 9.65.

Found % : C, 57.69 ; H, 6.82 ; N, 9.38.

Example 8

30 N-[4-[2-(Dimethylamino)ethoxy]benzyl]-4-sulfamoylbenzamide

To a cooled solution of 1.50 g of 4-[2-(dimethylamino)ethoxy]-benzylamine and 0.87 g of triethylamine in 10 ml of chloroform was added 1.87 g of 4-sulfamoylbenzyl chloride, which was prepared from 1.71 g of 4-sulfamoylbenzoic acid with 16.3 g of thionyl chloride in the usual way, with stirring. The mixture was stirred at room temperature for 30 minutes and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was washed with ethyl acetate to give 1.19 g of pale yellow crystals, which were recrystallized from ethanol to give colorless crystals, m.p. 173.5-174.5°C.

40 Analysis for $C_{18}H_{23}N_3O_4S$:

Calculated % : C, 57.28 ; H, 6.14 ; N, 11.13.

Found % : C, 57.58 ; H, 6.40 ; N, 10.95.

Example 9

45 N-[4-[2-(Dimethylamino)ethoxy]benzyl]-4-fluorobenzamide

To a cooled solution of 2.00 g of 4-[2-(dimethylamino)ethoxy]-benzylamine and 1.14 g of triethylamine in 10 ml of chloroform was added 1.80 g of 4-fluorobenzoyl chloride, which was prepared from 1.59 g of 4-fluorobenzoic acid with 7.77 g of thionyl chloride. The mixture was stirred for 30 minutes and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was washed with n-hexane to give 3.07 g of pale yellow crystals, which were recrystallized from a mixture of ethanol and ether to give colorless needles, m.p. 113-114.5°C.

55 Analysis for $C_{18}H_{21}FN_2O_2$:

Calculated % : C, 68.34 ; H, 6.69 ; N, 8.85.

Found % : C, 68.31 ; H, 6.67 ; N, 8.73.

Further, the free base was converted into the hydrochloride in the usual way. Recrystallization of the hydrochloride from ethanol gave colorless plates, m.p. 165-166°C.

Analysis for $C_{18}H_{21}FN_2O_2 \cdot HCl$:

5 Calculated % : C, 61.27 ; H, 6.28 ; N, 7.94.
 Found % : C, 61.18 ; H, 6.29 ; N, 7.75.

Examples 10

10 2-Amino-N-[4-[2-(dimethylamino)ethoxy]benzyl]benzamide

 To a solution of 2.00 g of 4-[2-(dimethylamino)ethoxy]benzylamine in 20 ml of ethyl acetate was added 1.04 g of isatoic anhydride. The mixture was stirred at room temperature for 15 minutes. Hydrochloric acid (10%) was added to the mixture. The aqueous layer was separated, made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. Recrystallization of the residue from ethyl acetate gave 1.85 g of colorless pillars, m.p. 104-105°C.

 Analysis for $C_{18}H_{23}N_3O_2$:

 Calculated % : C, 68.98 ; H, 7.40 ; N, 13.41.
 Found % : C, 69.07 ; H, 7.03 ; N, 13.32.

 In the same manner as described in Examples 1 to 10, the compounds of Examples 11 to 86 were prepared. The physical and chemical properties of the compounds of Examples 11 to 86 are shown in Tables 4 and

5.

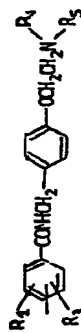
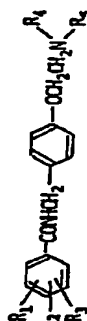
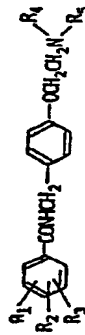


Table 4

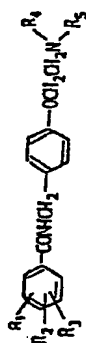
Example No.	R ₁	R ₂	R ₃	R ₄	R ₅	salt	crystals	melting point (solvent)	Analysis for	(Calcd. CHN; Found CHN;)
1 1	2-OH	3-OH	H	Me	Me	fumarate	colorless	122-123° (EtOH)	C ₂₀ H ₂₂ N ₂ O ₄ ·C ₄ H ₄ O ₄	60.75; 6.37; 5.80 60.61; 6.41; 5.78
1 2	2-OH	4-OH	H	Me	Me	—	needles	75-76° (EtOH-IPr ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	67.02; 7.31; 7.82 67.04; 7.26; 7.55
1 3	2-OH	6-OH	H	Me	Me	—	colorless	130-131° (AcOEt)	C ₂₀ H ₂₂ N ₂ O ₄	67.02; 7.31; 7.82 66.85; 7.29; 7.58
1 4	3-OH	5-OH	H	Me	Me	—	colorless	71-72° (EtOH-IPr ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	67.02; 7.31; 7.82 66.90; 7.12; 7.58
1 5	3,4- -O- -O-	—	H	Me	Me	—	colorless	89-90° (EtOH-IPr ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	66.65; 6.48; 8.18 66.61; 6.45; 8.02
	—	—	H	Me	Me	hydrochloride	colorless	166-167° (EtOH)	C ₂₀ H ₂₂ N ₂ O ₄ ·HCl	60.24; 6.12; 7.39 60.13; 6.21; 7.18
1 6	3-OH	4-OH	H	Me	Me	—	colorless	129.5-130.5° (AcOEt)	C ₂₀ H ₂₂ N ₂ O ₄	66.26; 7.02; 8.13 66.34; 7.05; 7.97
1 7	3,4- -O- -O-	—	H	-(CH ₂) ₂ -	—	—	yellow; needles	64-65° (AcOEt-IPr ₂ O)	C ₂₂ H ₂₄ N ₂ O ₄	59.09; 6.85; 7.32 59.05; 6.74; 7.19
1 8	3-OH	4-OH	H	-(CH ₂) ₂ -	—	—	colorless	83-85° (AcOEt-IPr ₂ O)	C ₂₂ H ₂₄ N ₂ O ₄	58.73; 7.34; 7.29 58.61; 7.38; 7.08
1 9	3-OH	4-OH	H	-(CH ₂) ₂ -	—	—	yellow	113-114° (AcOEt-IPr ₂ O)	C ₂₂ H ₂₄ N ₂ O ₄	59.32; 7.59; 7.03 59.49; 7.73; 6.97
2 0	H	H	H	Me	Me	—	colorless	84-85° (AcOEt-IPr ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	72.46; 7.43; 9.39 72.53; 7.25; 9.34
2 1	4-OH	H	H	Me	Me	—	plates	133-134° (EtOH)	C ₂₀ H ₂₂ N ₂ O ₄	58.77; 7.05; 8.81 59.04; 7.15; 8.85
2 2	2-OH	H	H	Me	Me	—	colorless	72.5-73.5° (IPr ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	59.49; 7.37; 8.53 59.40; 7.36; 8.32
	—	—	H	Me	Me	hydrochloride	colorless	166.5-157.5° (EtOH)	C ₂₀ H ₂₂ N ₂ O ₄ ·HCl	61.54; 6.91; 7.68 62.53; 6.99; 7.37
2 3	3-OH	H	H	Me	Me	—	colorless	66-68° (IPr ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	59.49; 7.37; 8.53 59.49; 7.13; 8.44
	—	—	H	Me	Me	malate	colorless	100-101° (IPr ₂ O-IPr ₂ O)	C ₂₂ H ₂₄ N ₂ O ₄ ·C ₄ H ₄ O ₄	57.15; 6.35; 6.30 62.02; 6.26; 6.35
2 4	4-OH	H	H	Me	Me	—	colorless	119-120° (EtOH-Et ₂ O)	C ₂₀ H ₂₂ N ₂ O ₄	59.49; 7.37; 8.53 59.47; 7.29; 8.42
	—	—	H	Me	Me	hydrochloride	colorless	175-176° (EtOH)	C ₂₀ H ₂₂ N ₂ O ₄ ·HCl	61.54; 6.91; 7.68 62.46; 6.97; 7.52
2 5	4-OEt	H	H	Me	Me	—	colorless	128-129° (AcOEt)	C ₂₂ H ₂₄ N ₂ O ₄	70.15; 7.65; 8.18 69.93; 7.75; 7.94
	—	—	H	Me	Me	hydrochloride	colorless	164-165° (EtOH-Et ₂ O)	C ₂₂ H ₂₄ N ₂ O ₄ ·HCl	63.40; 7.16; 7.39 63.15; 7.32; 7.22



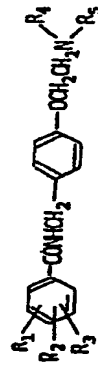
Example No.	R ₁	R ₂	R ₃	R ₄	salt	crystals	melting point (solvent)	Analysis for	(Calcd. C,H,N; Found C,H,N;)
26	4-OH-n	H	H	Me	Me	colorless scales	131-132° (AcOEt)	C ₁₁ H ₁₄ N ₂ O ₄	71.32; 8.16; 7.56 71.17; 8.26; 7.55
27	4-OH-n	H	H	-(CH ₂) ₄ -	—	colorless needles	120-121° (AcOEt)	C ₁₅ H ₂₀ N ₂ O ₄	71.16; 7.39; 7.00 70.93; 7.54; 7.97
28	4-OEt	H	H	-(CH ₂) ₄ -	—	colorless needles	125-127° (AcOEt)	C ₁₇ H ₂₂ N ₂ O ₄	71.31; 7.66; 7.60 71.57; 7.84; 7.52
29	3-OEt	H	H	Me	Me	colorless needles	80-81° (AcOEt)	C ₁₁ H ₁₄ N ₂ O ₄	70.15; 7.65; 8.18 70.03; 7.55; 8.05
30	4-OEt-n	H	H	Me	Me	colorless needles	117-119° (Pr ₂ O)	C ₁₁ H ₁₄ N ₂ O ₄	70.76; 7.92; 7.86 70.58; 7.93; 7.81
31	3-OH-n	4-OEt	H	Me	Me	colorless needles	113-114° (AcOEt)	C ₁₁ H ₁₄ N ₂ O ₄	67.72; 7.58; 7.52 67.66; 7.61; 7.50
32	3-OEt	4-OEt	H	Me	Me	colorless needles	127.5-129° (AcOEt)	C ₁₁ H ₁₄ N ₂ O ₄	68.37; 7.82; 7.25 68.39; 7.54; 7.11
33	3-OEt	5-OEt	H	Me	Me	colorless needles	114-114.5° (AcOEt)	C ₁₁ H ₁₄ N ₂ O ₄	68.37; 7.82; 7.25 68.15; 7.73; 7.20
34	2-OH-n	4-OH-n	5-Cl	-(CH ₂) ₄ -	—	colorless needles	144-146.5° (EtOH)	C ₁₁ H ₁₄ ClN ₂ O ₄	67.45; 6.49; 10.40 67.48; 6.56; 10.26
35	2-OH-n	4-OH-n	5-Cl	-(CH ₂) ₄ -	—	colorless needles	121-122° (AcOEt)	C ₁₁ H ₁₄ ClN ₂ O ₄	63.23; 6.75; 10.05 63.24; 6.80; 9.78
36	5-SO ₃ Me	2-OH-n	H	Me	Me	colorless needles	154-156° (AcOEt-EtOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S·1/2H ₂ O	55.80; 6.56; 9.76 56.10; 6.61; 9.77
37	5-SO ₃ Me	2-OH-n	H	-(CH ₂) ₄ -	—	colorless needles	91-93° (EtOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S·1/2H ₂ O	55.86; 6.47; 9.31 55.66; 6.35; 9.06
38	5-SO ₃ Me	2-OH-n	H	-(CH ₂) ₄ -	—	colorless needles	113-114° (EtOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S·H ₂ O	56.76; 6.71; 9.03 56.81; 6.74; 8.86
					hydrochloride	colorless needles	203-204° (MeOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S·HCl	54.09; 6.29; 8.60 53.98; 6.28; 8.39
39	3-SO ₃ Me	4-Cl	H	Me	Me	hydrochloride	146-147° (EtOH)	C ₁₁ H ₁₄ ClN ₂ O ₄ ·S·HCl	49.49; 5.81; 8.66 49.55; 5.83; 8.43
40	3-SO ₃ Me	4-Cl	H	-(CH ₂) ₄ -	Zincate	colorless needles	110-111° (EtOH)	C ₁₁ H ₁₄ ClN ₂ O ₄ ·S	51.03; 5.63; 7.11 52.79; 5.64; 6.96
41	5-SO ₃ Me	2-OH-n	4-OH-n	Me	Me	colorless needles	160-161° (EtOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S	51.89; 6.31; 12.88 52.49; 6.23; 12.86
					hydrochloride	colorless needles	134-136° (MeOH-AcOEt)	C ₁₁ H ₁₄ N ₂ O ₄ ·S·HCl	47.44; 6.13; 11.75 48.12; 6.27; 11.50
42	3-SO ₃ Me	2-OH-n	H	-(CH ₂) ₄ -	—	colorless needles	123-129° (EtOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S	59.55; 6.77; 9.10 59.49; 6.68; 9.10
43	5-SO ₃ Me	2-OH-n	H	-(CH ₂) ₄ -	—	colorless needles	165-169° (EtOH)	C ₁₁ H ₁₄ N ₂ O ₄ ·S	59.04; 6.53; 9.39 58.82; 6.24; 9.31



Example No.	R ₁	R ₂	R ₃	R ₄	R ₅	salt	crystals	melting point (solvent)	Analysis for	(Calcd. C; H; N; Found C; H; N;)
4 4	2-Cl	H	H	Me	Me	—	colorless needles	66-67° (IPr ₂ O)	C ₁₆ H ₁₅ ClN ₂ O ₂ · 1/4H ₂ O	64.09; 6.42; 8.30 64.24; 6.39; 8.07
4 5	3-Cl	H	H	Me	Me	hydrochloride	colorless scales	207-208° (EtOH)	C ₁₆ H ₁₅ ClN ₂ O ₂ · HCl	58.54; 6.00; 7.59 58.30; 6.07; 7.30
4 6	4-Cl	H	H	Me	Me	—	colorless needles	74-79° (IPr ₂ O)	C ₁₆ H ₁₅ ClN ₂ O ₂	64.98; 6.36; 7.59 65.02; 6.37; 8.18
4 7	3-Me	H	H	Me	Me	hydrochloride	colorless scales	165-167° (EtOH-Et ₂ O)	C ₁₆ H ₁₅ ClN ₂ O ₂ · HCl	58.54; 6.00; 7.59 58.27; 6.26; 7.28
4 8	4-Me	H	H	Me	Me	—	colorless needles	105-106° (EtOH-Et ₂ O)	C ₁₆ H ₁₅ ClN ₂ O ₂	64.96; 6.36; 8.42 65.05; 6.42; 8.24
4 9	4-Et	H	H	Me	Me	hydrochloride	colorless scales	165-168° (EtOH)	C ₁₆ H ₁₅ ClN ₂ O ₂ · HCl	58.54; 6.00; 7.59 58.46; 6.21; 7.22
5 0	2-HO	H	H	Me	Me	—	colorless plates	118-120° (EtOH-Me ₂ CO)	C ₁₆ H ₁₅ N ₂ O ₂ · HCl	65.41; 7.22; 8.03 65.25; 7.19; 7.83
5 1	3-HO	H	H	Me	Me	—	colorless needles	109-110° (IPr ₂ O)	C ₁₆ H ₁₅ N ₂ O ₂	73.05; 7.74; 8.97 73.16; 7.61; 8.78
5 2	4-HO	H	H	Me	Me	hydrochloride	colorless needles	197-199° (EtOH-Et ₂ O)	C ₁₆ H ₁₅ N ₂ O ₂ · HCl	65.41; 7.22; 8.03 65.20; 7.32; 7.70
5 3	4-CN	H	H	Me	Me	—	colorless needles	101-102° (IPr ₂ O)	C ₁₆ H ₁₅ N ₂ O ₂	73.58; 8.03; 8.58 73.65; 7.98; 8.35
5 4	4-tBu	H	H	Me	Me	—	pale yellow needles	88-89° (AcOEt-Et ₂ O)	C ₁₆ H ₁₅ N ₂ O ₂ · HCl	56.92; 5.84; 11.06 56.91; 6.05; 10.82
5 5	4-CH ₃	H	H	Me	Me	—	pale yellow needles	204-205° (EtOH)	C ₁₆ H ₁₅ N ₂ O ₂ · HCl	62.96; 6.16; 12.24 62.90; 6.24; 12.18
5 6	4-CH ₃	H	H	Me	Me	—	pale yellow needles	153-154° (AcOEt)	C ₁₆ H ₁₅ N ₂ O ₂	62.96; 6.16; 12.24 62.94; 6.13; 12.16
5 7	4-CH ₃	H	H	Me	Me	—	pale yellow needles	83-84° (AcOEt-Et ₂ O)	C ₁₆ H ₁₅ N ₂ O ₂	70.57; 6.35; 12.99 70.41; 6.42; 12.71
5 8	4-CH ₃	H	H	Me	Me	hydrochloride	pale yellow needles	182-183° (EtOH)	C ₁₆ H ₁₅ N ₂ O ₂ · HCl · 1/4H ₂ O	52.63; 6.12; 11.53 52.94; 6.13; 11.23
5 9	4-CH ₃	H	H	Me	Me	—	colorless needles	135-137° (AcOEt)	C ₁₆ H ₁₅ N ₂ O ₂	74.54; 8.53; 7.90 74.50; 8.28; 7.86
6 0	4-CH ₃	H	H	Me	Me	—	colorless needles	144-146° (AcOEt)	C ₁₆ H ₁₅ N ₂ O ₂	70.35; 7.97; 12.31 70.21; 7.56; 12.02
6 1	4-CH ₃	H	H	Me	Me	—	colorless needles	165-167° (AcOEt)	C ₁₆ H ₁₅ N ₂ O ₂	74.53; 7.74; 8.28 74.63; 7.44; 8.15
6 2	4-CH ₃	H	H	Me	Me	—	prisms	102-103° (AcOEt)	C ₁₆ H ₁₅ N ₂ O ₂	72.18; 6.63; 12.03 71.96; 6.49; 11.80



Example No.	R ₁	R ₂	R ₃	R ₄	salt	crystals	melting point (solvent)	analysis for	(Calcd. C:H:N, Found C:H:N)
58	3-NO ₂	H	H	-(CH ₂) ₄ -	hydrochloride	grayish brown needles	176-178° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂ ·HCl	59.18; 5.96; 10.35 59.30; 5.97; 10.39
59	2-Cl	4-Cl	H	He	—	colorless needles	111-112° (C ₆ H ₆)	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₂	58.87; 5.49; 7.63 58.89; 5.46; 7.58
60	3-Cl	4-Cl	H	He	hydrochloride	colorless scales	218-219° (EtOH)	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₂ ·HCl	53.55; 5.24; 6.94 53.41; 5.39; 6.76
61	3-Cl	5-Cl	H	He	hydrochloride	colorless needles	209.5-212° (MeOH)	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₂ ·HCl	53.55; 5.24; 6.94 53.75; 5.47; 6.89
62	3-NO ₂	4-NO ₂	H	He	—	colorless needles	159-160° (EtOH)	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₂ ·HCl	53.55; 5.24; 6.94 53.46; 5.46; 6.71
63	3-NO ₂	4-NO ₂	H	He	hydrochloride	yellow needles	88-90° (EtOH)	C ₁₈ H ₁₄ N ₂ O ₂	63.85; 6.48; 11.76 63.56; 6.61; 11.70
64	4-NO ₂	4-NO ₂	H	He	—	colorless prisms	170-171° (EtOH-Et ₂ O)	C ₁₈ H ₁₄ N ₂ O ₂ ·HCl	57.94; 6.14; 10.67 57.66; 6.38; 10.63
65	2-OEt	H	H	-(CH ₂) ₄ -	—	pale yellow prisms	113-114° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂	65.78; 6.57; 10.96 65.49; 6.64; 10.87
66	2-OH	H	H	-(CH ₂) ₄ -	—	colorless needles	90-91° (IP ₂ O)	C ₁₈ H ₁₆ N ₂ O ₂	74.97; 8.01; 7.95 74.93; 7.81; 7.85
67	3-OH	H	H	He	hydrochloride	colorless prisms	127-130° (EtOH-Et ₂ O)	C ₁₈ H ₁₆ N ₂ O ₂ ·HCl	63.40; 7.18; 7.39 63.14; 7.32; 7.40
68	3-SO ₂ Me	H	H	He	hydrochloride	colorless needles	153-156° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂ ·HCl	61.62; 6.61; 7.98 61.63; 6.66; 7.95
69	2-NO ₂	H	H	He	—	colorless plates	151-153° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂	68.77; 7.05; 8.91 68.94; 7.21; 8.96
70	2-F	H	H	He	hydrochloride	colorless crystals	169-172° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂ ·HCl	57.28; 6.14; 11.13 57.30; 6.07; 11.12
71	3-F	H	H	He	—	colorless needles	186-187.5° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂ ·HCl	65.41; 7.22; 8.03 65.34; 7.14; 8.00
72	3-NO ₂	H	H	He	—	colorless needles	70-72° (EtOH-Et ₂ O)	C ₁₈ H ₁₆ N ₂ O ₂	68.34; 6.89; 8.85 68.24; 6.57; 8.82
73	3-NO ₂	H	H	He	hydrochloride	colorless needles	139-142° (EtOH-Et ₂ O)	C ₁₈ H ₁₆ N ₂ O ₂ ·HCl	61.27; 6.28; 7.94 61.25; 6.30; 7.92
74	3-NO ₂	H	H	He	—	colorless needles	86-87° (IP ₂ O)	C ₁₈ H ₁₆ N ₂ O ₂	68.34; 6.89; 8.85 68.34; 6.66; 8.82
75	3-NO ₂	H	H	He	—	colorless needles	127-128° (EtOH)	C ₁₈ H ₁₆ N ₂ O ₂ ·C ₆ H ₅ O ₂	61.10; 5.13; 6.48 60.94; 5.88; 6.50
76	3-NO ₂	H	H	He	hydrochloride	colorless crystals	173-174° (MeOH-EtOH)	C ₁₈ H ₁₆ N ₂ O ₂ ·2HCl	55.86; 6.52; 10.88 56.13; 6.49; 10.89



Example No.	R ₁	R ₂	R ₃	R ₄	substit	crystals	melting point (solvent)	Analysis for	(Calcd. C:H:N; Found C:H:N)
7 3	4-NH ₂	H	H	Me	hydrochloride	colorless needles	171-173° (MeOH)	C ₁₂ H ₁₂ N ₂ O ₂ ·2HCl	55.96; 6.52; 10.88 55.89; 6.69; 10.88
7 4	3-CN	H	H	Me	—	colorless crystals	88-100° (AcOEt-IPr ₂ O)	C ₁₂ H ₁₂ N ₂ O ₂	70.57; 6.55; 12.99 70.65; 6.51; 12.89
7 5	3-tBu	4-OH	5-tBu	Me	hydrochloride	colorless prisms	155-157° (EtOH)	C ₁₂ H ₁₂ N ₂ O ₂ ·HCl	53.42; 6.16; 11.68 53.32; 6.14; 11.73
7 6	3-Cl	4-NH ₂	5-Cl	Me	—	colorless plates	142-144° (Me ₂ CO-IPr ₂ O)	C ₁₂ H ₁₂ N ₂ O ₂	73.20; 8.98; 6.57 73.47; 8.96; 6.29
7 7	3-Cl	4-NH ₂	5-Cl	Me	hydrochloride	pale brown needles	132-134° (EtOH)	C ₁₂ H ₁₂ Cl ₂ N ₂ O ₂ ·HCl ·1/2H ₂ O	50.54; 5.42; 9.82 50.55; 5.51; 9.78
7 8	2-F	4-F	5-F	Me	—	pale brown needles	83-84° (AcOEt)	C ₁₂ H ₁₂ Cl ₂ N ₂ O ₂	58.83; 5.68; 10.29 58.00; 6.04; 10.19
					—	colorless prisms	80-82° (AcOEt)	C ₁₂ H ₁₂ F ₂ N ₂ O ₂	51.36; 5.44; 7.95 51.32; 5.71; 7.98

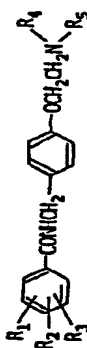
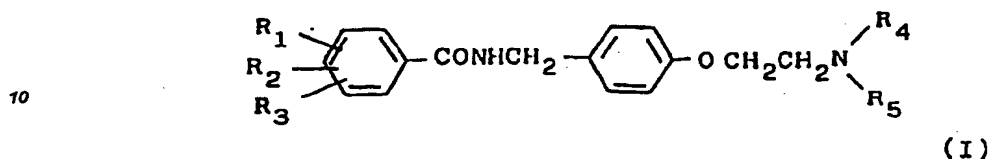


Table 5

Example No.	R ₁	R ₂	R ₃	R ₄	R ₅	IR spectrum ν (1/g)cm ⁻¹	MS spectrum m/z (H ⁺)	Color	NMR spectrum δ (CDCl ₃)ppm
79	3-OH	H	H	-(CH ₂) ₄ -		1650 (C=O)	354	yellow oil	1.66-1.98(4H,m), 2.44-2.76(4H,m), 2.88(2H,t,J=6Hz), 3.82(3H,s), 4.09(2H,t,J=6Hz), 4.61(2H,d,J=5.5Hz), 6.47(1H,br), 6.97(2H,d,J=9Hz), 7.20-7.38(6H,m)
80	3-SO ₂ NH ₂	4-Cl	H	Me	Me	1648 (C=O)	413,411 (1:3)	pale yellow oil	2.29(6H,s), 2.69(2H,t,J=5.5Hz), 3.92(2H,br), 3.89(2H,t,J=5.5Hz), 4.47(2H,d,J=5.5Hz), 6.78(2H,d,J=9Hz), 7.07(1H,t,J=5.5Hz), 7.49(1H,d,J=8.5Hz), 7.92(1H,dd,J=8.5,2Hz), 8.32(1H,d,J=2Hz)
81	3-SO ₂ NH-Me	4-Cl	H	Me	Me	1650 (C=O)	427,425 (1:3)	colorless oil	2.32(6H,s), 2.62(3H,s), 2.71(2H,t,J=5.5Hz), 4.04(2H,t,J=5.5Hz), 4.54(2H,d,J=5.5Hz), 5.88(1H,br), 6.85(2H,d,J=9Hz), 7.25(2H,d,J=9Hz), 7.56(1H,d,J=8.5Hz), 7.99(1H,dd,J=8.5,2Hz), 8.39(1H,d,J=2Hz)
82	3-SO ₂ NH ₂	4-Cl	H	-(CH ₂) ₄ -		1644 (C=O)	439,437 (1:3)	yellow oil	1.55-1.97(4H,m), 2.32-2.77(4H,m), 2.87(2H,t,J=6Hz), 4.07(2H,t,J=6Hz), 4.52(2H,br), 6.82(2H,d,J=9Hz), 7.09(2H,d,J=9Hz), 7.36(1H,d,J=8.5Hz), 7.70(1H,br), 7.83(1H,dd,J=8.5,2Hz), 8.34(1H,d,J=2Hz)
83	3-SO ₂ NH-Me	4-Cl	H	-(CH ₂) ₄ -		1644 (C=O)	453,451 (1:3)	yellow oil	1.57-1.98(4H,m), 2.34-2.77(4H,m), 2.88(2H,t,J=5.5Hz), 4.08(2H,t,J=5.5Hz), 4.53(2H,d,J=5.5Hz), 6.84(2H,d,J=9Hz), 7.10(1H,br), 7.25(2H,d,J=9Hz), 7.55(1H,d,J=8.5Hz), 8.03(1H,dd,J=8.5,2Hz), 8.40(1H,d,J=2Hz)
84	3-SO ₂ N-Me	4-OH	H	Me	Me	1644 (C=O)	435	colorless oil	2.32(6H,s), 2.71(2H,t,J=5.5Hz), 2.82(6H,s), 3.95(3H,s), 4.04(2H,t,J=5.5Hz), 4.53(2H,d,J=5.5Hz), 6.86(2H,d,J=9Hz), 7.03(1H,d,J=8.5Hz), 7.27(2H,d,J=9Hz), 8.10(1H,dd,J=8.5,2Hz), 8.25(1H,d,J=2.5Hz)
85	3-SO ₂ N-Me	4-OH	H	-(CH ₂) ₄ -		1645 (C=O)	461	pale yellow oil	1.62-1.89(4H,m), 2.45-2.75(4H,m), 2.83(6H,s), 2.89(2H,t,J=6Hz), 3.96(3H,s), 4.10(2H,t,J=6Hz), 4.55(2H,d,J=5.5Hz), 6.88(2H,d,J=9Hz), 7.05(1H,d,J=8.5Hz), 7.27(2H,d,J=9Hz), 8.12(1H,dd,J=8.5,2Hz), 8.22(1H,d,J=2Hz)
86	2-F	4-F	5-F	-(CH ₂) ₄ -		1660 (C=O)	378	yellow oil	1.57-2.10(4H,m), 2.46-2.80(4H,m), 2.90(2H,t,J=6Hz), 4.10(2H,t,J=6Hz), 4.48-4.72(2H,m), 6.67-7.14(2H,m), 6.89(2H,d,J=9Hz), 7.25(2H,d,J=9Hz), 7.73-8.13(1H,m)

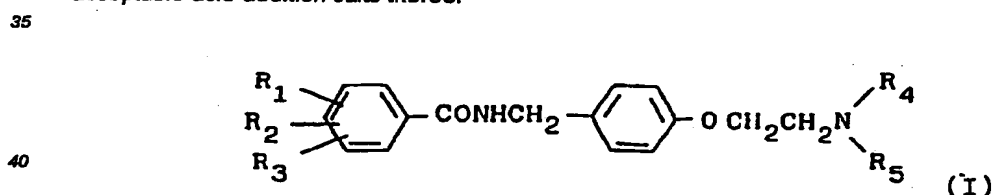
Claims

- 5 1. Amide-compound selected from those represented by the formula (I),

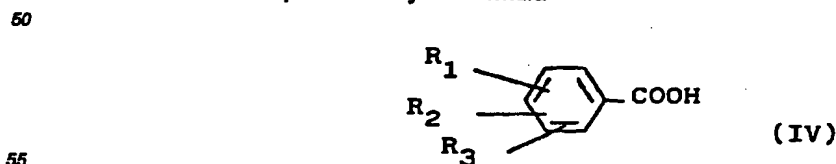


15 wherein R₁ represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R₂ represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, and wherein R₁ and R₂ can be combined to form methylenedioxy R₃ means hydrogen, lower alkyl, halogen, or amino, and wherein R₄ and R₅ may be the same or different and each represents lower alkyl and wherein R₄ and R₅ may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, and pharmacologically-acceptable acid-addition salts thereof.

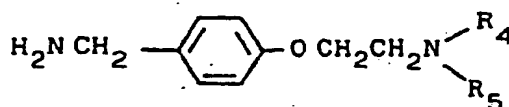
- 20 2. A compound of claim 1 which is N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide.
 3. A compound of claim 1 which is N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride.
 4. A compound of claim 1 which is 3,4-Methylenedioxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl] benzamide.
 5. A compound of claim 1 which is 3,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide.
 25 6. A compound of claim 1 which is N-[4-[2-(dimethylamino)ethoxy]benzyl]-4-ethoxy-3-methoxybenzamide.
 7. A compound of claim 1 which is N-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamide.
 8. A compound of claim 1 which is 4-Amino-5-chloro-2-methoxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide.
 30 9. A pharmaceutical composition useful to activate gastric motor function comprising one or more compounds as claimed in claims 1-8, in an amount effective for such purpose, together with a compatible, pharmaceutically-acceptable carrier or coating.
 10. A process for preparing amide-compounds represented by the formula (I) and pharmacologically-acceptable acid-addition salts thereof



45 wherein R₁ represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R₂ represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, and R₁ and R₂ can be combined to form methylenedioxy, R₃ means hydrogen, lower alkyl, halogen, or amino, R₄ and R₅ may be the same or different and each represents lower alkyl or R₄ and R₅ may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, which comprises reacting a functional derivative such as the chloride or other halide, the anhydride or a mixed anhydride, of a carbonic acid represented by the formula



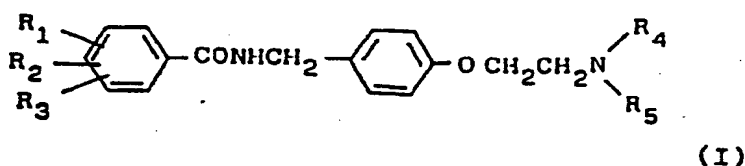
wherein R₁, R₂ and R₃ each has the same meaning as described above, with an amino-compound presented by the following formula,



wherein R_4 and R_5 each has the same meaning as described above, in the presence or in the absence of a base and in the presence of an organic solvent.

Patentansprüche

1. Amid-Verbindung, ausgewählt aus solchen der Formel (I)



in der R_1 Wasserstoff, Niederalkoxy, Hydroxy, Niederalkyl, Halogen, Amino, das durch Niederalkyl substituiert sein kann, Nitro, Cyano, Sulfamoyl, das durch Niederalkyl substituiert sein kann, bezeichnet, R_2 Wasserstoff, Niederalkoxy, Hydroxy, Niederalkyl, Halogen, Amino, Nitro bezeichnet und in der R_1 und R_2 miteinander unter Bildung von Methylendioxy kombiniert sein können, R_3 Wasserstoff, Niederalkyl, Halogen oder Amino bezeichnet und in der R_4 und R_5 gleich oder verschieden sein können und jeweils Niederalkyl bezeichnen und in der R_4 und R_5 zusammen mit Stickstoff unter Bildung von 1-PyrrolidinyI oder Piperidino kombiniert sein können, und deren pharmakologisch annehmbare Säure-Additionssalze.

2. Verbindung nach Anspruch 1, die N-[4-[2-(Dimethylamino)-ethoxy]benzyl]-3,4-dimethoxybenzamid ist.

3. Verbindung nach Anspruch 1, die N-[4-[2-(Dimethylamino)-ethoxy]benzyl]-3,4-dimethoxybenzamid-hydrochlorid ist.

4. Verbindung nach Anspruch 1, die 3,4-Methylendioxy-N-[4-[2-(1-pyrrolidinyI)ethoxy]benzyl]benzamid ist.

5. Verbindung nach Anspruch 1, die 3,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyI)ethoxy]benzyl]benzamid ist.

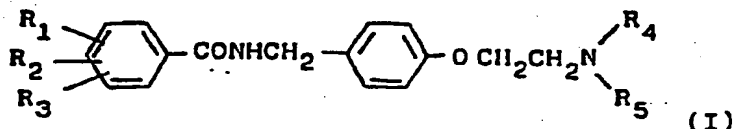
6. Verbindung nach Anspruch 1, die N-[4-[2-(Dimethylamino)-ethoxy]benzyl]-4-ethoxy-3-methoxybenzamid ist.

7. Verbindung nach Anspruch 1, die N-[4-[2-(Dimethylamino)-ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamid ist.

8. Verbindung nach Anspruch 1, die 4-Amino-5-chloro-2-methoxy-N-[4-[2-(1-pyrrolidinyI)ethoxy]benzyl]benzamid ist.

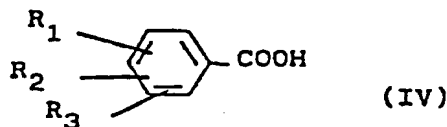
9. Pharmazeutische Zusammensetzung, die zur Aktivierung der gastromotorischen Funktion geeignet ist, umfassend eine oder mehrere Verbindungen, wie sie in den Ansprüchen 1 bis 8 beansprucht werden, in einer für einen derartigen Zweck wirksamen Menge zusammen mit einem kompatiblen, pharmazeutisch annehmbaren Träger oder Überzug.

10. Verfahren zur Herstellung von Amid-Verbindungen der Formel (I) und von deren pharmazeutisch annehmbaren Säure-Additionssalzen

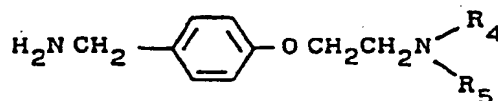


in der R_1 Wasserstoff, Niederalkoxy, Hydroxy, Niederalkyl, Halogen, Amino, das durch Niederalkyl substituiert sein kann, Nitro, Cyano, Sulfamoyl, das durch Niederalkyl substituiert sein kann, bezeichnet, R_2 Wasserstoff, Niederalkoxy, Hydroxy, Niederalkyl, Halogen, Amino, Nitro bezeichnet und in der R_1 und R_2 miteinander unter Bildung von Methylendioxy kombiniert sein können, R_3 Wasserstoff, Niederalkyl, Halogen oder Amino bezeichnet und in der R_4 und R_5 gleich oder verschieden sein können und jeweils Niederalkyl bezeichnen und in der

R_4 und R_5 zusammen mit Stickstoff unter Bildung von 1-PyrrolidinyI oder Piperidino kombiniert sein können, umfassend die Umsetzung eines funktionellen Derivats wie des Chlorids oder eines anderen Halogenids, des Anhydrids oder eines gemischten Anhydrids einer Carbonsäure der Formel



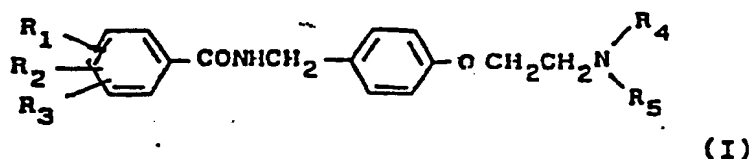
10 in der R_1 , R_2 und R_3 jeweils die im Vorstehenden beschriebenen Bedeutungen haben, mit einer Amino-Verbindung der nachstehenden Formel



20 in der R_4 und R_5 jeweils die im Vorstehenden beschriebenen Bedeutungen haben, in Anwesenheit oder in Abwesenheit einer Base und in Gegenwart eines organischen Lösungsmittels.

Revendications

25 1. Composé amide choisi parmi ceux représentés par la formule (I),



35 dans laquelle R_1 représente un hydrogène, un alcoxy inférieur, un hydroxy, un alcoyle inférieur, un halogène, un amino qui peut être substitué par un alcoyle inférieur, un nitro, un cyano, un sulfamoyle qui peut être substitué par un alcoyle inférieur, R_2 représente un hydrogène, un alcoxy inférieur, un hydroxy, un alcoyle inférieur, un halogène, un amino, un nitro, et dans laquelle R_1 et R_2 peuvent être combinés pour former un méthylène-dioxy, R_3 représente un hydrogène, un alcoyle inférieur, un halogène ou un amino, et dans laquelle R_4 et R_5 peuvent être identiques ou différents et chacun représente un alcoyle inférieur et dans laquelle R_4 et R_5 peuvent être combinés ensemble avec l'azote pour former le 1-pyrrolidinyI ou piperidino et les sels acides pharmacologiquement acceptables de celui-ci.

2. Un composé de la revendication 1 qui est le N-[4-[2-(diméthylamino)éthoxy]-benzyl]-3,4-diméthoxybenzamide.

45 3. Un composé de la revendication 1 qui est le chlorhydrate de N-[4-[2-(diméthylamino)éthoxy]-benzyl]-3,4-diméthoxybenzamide.

4. Un composé de la revendication 1 qui est le 3,4-méthylènedioxy-N-[4-[2-(1-pyrrolidinyI)éthoxy]benzyl]benzamide.

5. Un composé de la revendication 1 qui est le 3,4-diméthoxy-N-[4-[2-(1-pyrrolidinyI)éthoxy]benzyl]benzamide.

6. Un composé de la revendication 1 qui est le N-[4-[2-(diméthylamino)éthoxy]-benzyl]-4-éthoxy-3-méthoxybenzamide.

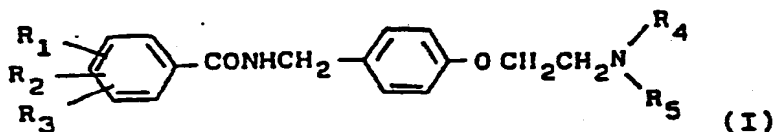
7. Un composé de la revendication 1 qui est le N-[4-[2-(diméthylamino)-éthoxy]benzyl]-2-méthoxy-5-sulfamoylbenzamide.

55 8. Un composé de la revendication 1 qui est le 4-amino-5-chloro-2-méthoxy-N-[4-[2-(1-pyrrolidinyI)éthoxy]benzyl]benzamide.

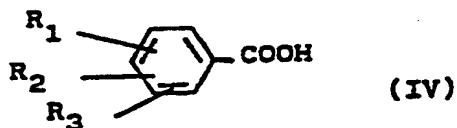
9. Une composition pharmaceutique utilisée pour activer la fonction motrice gastrique comprenant un ou plusieurs composés tels que revendiqués dans les revendications 1-8, dans une quantité efficace pour un tel

but ensemble avec un support ou une enveloppe compatibles, pharmaceutiquement acceptables.

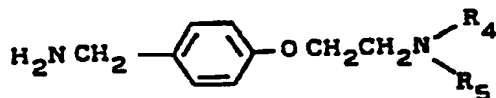
10. Un procédé pour préparer des composés amide représentés par la formule (I) et les sels d'addition acide pharmacologiquement acceptables de ceux-ci,



dans laquelle R_1 représente un hydrogène, un alcoyle inférieur, un hydroxy, un alcoyle inférieur, un halogène, un amino qui peut être substitué par un alcoyle inférieur, un nitro, un cyano, un sulfamoyle qui peut être substitué par un alcoyle inférieur, R_2 représente un hydrogène, un alcoyle inférieur, un hydroxy, un alcoyle inférieur, un halogène, un amino, un nitro, et dans laquelle R_1 et R_2 peuvent être combinés pour former un méthylène-dioxy, R_3 représente un hydrogène, un alcoyle inférieur, un halogène ou un amino, R_4 et R_5 peuvent être identiques ou différents et chacun représente un alcoyle inférieur et dans laquelle R_4 et R_5 peuvent être combinés ensemble avec l'azote pour former le 1-pyrrolidinyl ou piperidino, qui comprend la réaction d'un dérivé fonctionnel tel que le chlorure ou un autre haloïde, de l'anhydride ou d'un anhydride mixte, d'un acide carbonique représenté par la formule,



dans laquelle R_1 , R_2 et R_3 ont chacun la même signification que ce qui a été décrit ci-dessus, avec un composé amino représenté par la formule suivante,



dans laquelle R_4 et R_5 ont chacun la même signification que celle décrite ci-dessus, en présence ou en absence d'une base et en présence d'un solvant organique.

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